PUBLIC CITIZEN HEALTH RESEARCH GROUP

Comments Before The

Food and Drug Administration's Drug Safety and Risk Management Advisory Committee

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In June 1998, Public Citizen petitioned the FDA to ban the distribution of dangerously misleading prescription drug information to the public by pharmacists.[1] We argued that drugs were misbranded when dispensed with inaccurate or misleading information. Cosigners of the petition were the parents of seven-year-old Cory Christen who died from a drug-induced cardiac arrhythmia. His death was needless and preventable and is directly attributable to his parents being deprived of vital dosing and adverse reaction information, information that was omitted from a patient information leaflet produced by an unregulated commercial information vendor, Medi-Span, Inc. of Indianapolis, for the antidepressant drug imipramine (Tofranil).

The Food and Drug Administration's (FDA) characterization of the results of the *Evaluation of Written Prescription Information Provided in Community Pharmacies, 2001* [2] study (the 2001 Evaluation) as showing the private sector making "progress in meeting the goals" of providing the public with useful written prescription drug information is disgraceful. Likewise, the finding that "the overwhelming majority of pharmacy-generated leaflets adhered fully" to the criterion of being scientifically accurate is appalling and is apparently a failure of the study's authors, and the FDA, to read and understand the definition of scientifically accurate as defined in the 1996 *Action Plan for the Provision of Useful Prescription Medicine Information*[3] (The Action Plan).

The Action Plan is the legal basis for the evaluation of the quality of written information being distributed to consumers by pharmacists and was agreed to by commercial information vendors, trade lobbies representing pharmacy and medicine, and consumer groups.

If the FDA and the study's authors had adhered to The Action Plan, their conclusion would have been simple: No prescription drug consumer who gets one of these patient information leaflets is receiving written drug information that meets the minimum acceptable quality standards of The Action Plan.

Public Citizen was a member of the steering committee that negotiated The Action Plan in December 1996 and the plan is very clear as to what constitutes acceptable information that will count toward the quantitative goal of 75 percent of consumers receiving useful drug information:

1. The written information that meets these guidelines "– i.e., adheres to the criteria, includes the suggested components, and substantially conforms with the formatting suggestions here and in Appendix G – will be deemed 'useful' information and will 'count' toward the quantitative goals of the Plan." (page 16 of The Action Plan)

2. Information that "... adheres to the criteria, includes the suggested components, and substantially conforms to the guidelines in Chapter 3, will count toward meeting the goals of the Action Plan. (page 28 of The Action Plan)

Public Law 104-180 was enacted in 1995 and led to The Action Plan. This law required The Action Plan to "Achieve goals consistent with the goals" of the FDA's 1995 proposed Medication Guide rule.[4] The agency's stated standard for the determination of information usefulness was:

> Each sample [patient information leaflet] will be scored on each criterion, using "acceptable" and "not acceptable" cutoff points. ..., FDA believes that for a particular information sheet to be judged as acceptable overall, it must receive an acceptable rating on each of the individual components. (Medication Guide rule page 44201)

During the highly contentious debate that resulted in The Action Plan, "partial credit" was not envisioned, discussed or agreed to by the steering committee for patient information leaflets distributed by pharmacists. It is impossible to comprehend any usefulness for patient safety information that on average contains only 50 percent of the minimum required information as documented in the FDA's 2001 Evaluation. In fact, safety information that is incomplete is misleading and potentially dangerous.

PRIVATE SECTOR PROGRESS

Since the FDA's resurrection with the 1995 Medication Guide rule of a 1979 proposed rule[5] to require patient package inserts (PPIs), based primarily on a drug's approved product labeling, there have been at least five surveys or systematic examinations of the quality of patient information leaflets (PILs) distributed by pharmacists.

August 1995 – In their 1995 proposed Medication Guide rule, the agency examined the adequacy of written drug information produced by eight commercial information vendors being distributed by pharmacists to patients. The accuracy and comprehensiveness of the information for three drugs was determined by an assessment of consistency with

the drug's approved product labeling. By any estimate the private sector failed. For example, none of the eight vendors mentioned the contraindication for the use of enalapril (Vasotec) when allergic reactions or angioedema occurred during previous treatment with similar drugs.[6] This is potentially life-saving information.

April 1996 – A study to assess whether 50 Washington, DC pharmacies would simultaneously dispense prescriptions for the potentially life-threatening combination of erythromycin and terfenadine (Seldane) found that of 10 pairs of prescriptions filled without comment by chain pharmacies, nine were accompanied by written information that did not contain specific information about the interaction. No written information was provided by the five independent pharmacies that filled the prescriptions.[7]

The PILs collected in this study were clearly not consistent with the approved labeling for terfenadine. A black box warning had been added to terfenadine's labeling in January 1993 that warned of the drug's potentially fatal drug interaction with erythromycin.[8] In May 1993 patient labeling was added to the drug's professional product labeling. This information specifically warned the public in upper case bold letter not to use terfenadine with erythromycin. Patients were also warned that this interaction could cause death.[9] The FDA's and the manufacturer's expectations were that this information would be provided to patients by pharmacists.

The commercial information vendors voluntarily chose not to include this information in their leaflets and pharmacists voluntarily chose to dispense unregulated PILs that omitted life-saving information rather than distributing the FDA approved patient labeling for terfenadine that warned of the erythromycin drug interaction.

April 1997 – Public Citizen obtained PILs for 15 different nonsteroidal anti-inflammatory drugs (NSAIDs) distributed by pharmacists. A total of 59 leaflets produced by four commercial information vendors were evaluated using four criteria based on the FDA's 1995 proposed Medication Guide rule. None of the private sector leaflets met the criteria.[10]

April 1998 – In a study conducted by Public Citizen, 15 licensed pharmacists evaluated the PILs for five fluoroquinolone antibiotics produced by four unregulated commercial information vendors according to Scientific Accuracy criterion of The Action Plan. The information content of these PILs was not satisfactory to meet the scientific accuracy criterion as defined in The Action Plan.[11]

March 2000 – Public Citizen commented on the methodological inadequacy of the *Evaluation of Written Prescription Information Provided in Community Pharmacies: An 8-State Survey* (the 2000 Survey).[12] This was an interim survey funded by the FDA that was required by The Action Plan and conducted by the same principle investigator as the 2001 Evaluation.[13]

Despite the shortcomings of the FDA-funded survey's design, only 12.5 percent of the PILs distributed with the drug ibuprofen (Motrin) informed consumers of the drug's contraindications and only 5.3 percent included specific precautions, their significance, and how consumers could avoid harm.

Rather than demonstrating progress as the FDA seems to believe, the private sector has shown a consistent inability over the years to produce useful drug information according to agreed upon guidelines.

SCIENTIFIC ACCURACY

The authors of 2001 Evaluation, as they did in their 2000 Survey, either failed to read or comprehend The Action Plan's simple definition of scientifically accurate: Information consistent with or derived from FDA-approved labeling. (page 17 of The Action Plan)

The following are single examples of the lack of scientific accuracy found in the private sector leaflets for each of drugs involved in the 2001 Evaluation for Criterion 4 – specific precautions and how to avoid harm. The 2000 Physicians' Desk Reference was used as the source for the professional product labeling for these drugs.

Atenolol (Tenormin)

The professional product labeling for atenolol contains a box warning regarding the abrupt cessation of the drug: "Severe exacerbation of angina and the occurrence of myocardial infarction and ventricular arrhythmias have been reported in angina patients following the abrupt discontinuation of therapy with beta blockers."[14]

These leaflets were evaluated for containing the sub-criterion: Do not stop suddenly; gradual dose reduction may be needed. Only 35.8 percent of leaflets fully complied. Remarkably, 90.4 percent of these leaflets were scored as being scientifically accurate in the 2001 Evaluation.

Glyburide (DiaBeta)

The professional product labeling for glyburide contains the following statement in the Drug Interactions section of the label: "Certain drugs tend to produce hyperglycemia and may lead to loss of control. These drugs include the thiazides ...."[15]

These leaflets were evaluated for containing the sub-criterion about the use of glyburide with thiazide diuretics. Only 0.6 percent of leaflets fully complied. Overall, 96.4 percent of these leaflets were deemed scientifically accurate in the 2001 Evaluation.

Atorvastatin (Lipitor)

The professional product labeling for atorvastatin contains the following in the Warnings section of the label: "The risk of myopathy during treatment with other drugs in this class is increased with concurrent administration of ... erythromycin ...."[16]

These leaflets were evaluated for containing the sub-criterion about the use of atorvastatin in combination with the antibiotic erythromycin. Only 26.5 percent of these leaflets were fully compliant. Almost 100 percent (98.5%) of these leaflets were found to be scientifically accurate.

Nitroglycerin (Nitrostat)

The professional product labeling for nitroglycerine clearly indicates that the use of nitroglycerine and sildenafil together is contraindicated.[17]

These leaflets were evaluated for containing the sub-criterion about the use of nitroglycerin in combination with sildenafil (Viagra). Only 32.7 percent of these leaflets were fully compliant. Unbelievably, 99.1 percent of these leaflets were found to be scientifically accurate.

These leaflets omitted the majority of the important safety information that is available in the labels for these drugs. The FDA and the authors of the 2001 Evaluation are negligent in portraying to the public that the majority of these leaflets are scientifically accurate.

We are now 22 years past the private sector's promise to develop a variety of systems that would meet the goals of the FDA's 1979 proposed rule that would have required patient package inserts (PPIs) for ten classes of prescription drugs. This proposed rule has a familiar ring. Manufacturers would write the PPIs and pharmacists would have been required to distribute them to patients. The PPI would be based primarily on a drug's approved product labeling, it would be written in nontechnical language, and it would not be promotional in tone or content.

Spearheaded by trade groups representing pharmacy and medicine, a lobbying effort was undertaken that caused the PPI regulation to be among the most controversial issued in the last months of the Carter Administration. Needless to say, consumers favored the proposed PPI program. The day after President Reagan's inauguration in 1981, the White House called the FDA to make it clear that the PPI regulation was not to be enforced.[18] This would not be the last time an elected representative of the people would attempt to prevent the public access to high quality written drug information. On two occasions in the recent past, Michael Crapo of Idaho penned legislative language to prohibit the FDA from implementing the Medication Guide rule.[19]

In 1982, the FDA officially rescinded the regulation in favor of a voluntary plan. Private sector initiative commenced with the formation of the National Council on Patient Information and Education (NCPIE) and the consistent failure of the private sector to deliver what was promised culminating in the *Evaluation of Written Prescription Information Provided in Community Pharmacies, 2001.*

RECOMMENDATIONS

The failure of the private sector to meet the quality goals established in The Action Plan and thus the failure to achieve the distribution goal of 75 percent of patients getting scientifically accurate information leaves only one option under Public Law 104-180: "... the Secretary [Department of Health and Human Services] shall seek public comment on other initiatives that may be carried out to meet such goals."

We urge the Drug Safety and Risk Management Advisory Committee make a single recommendation to the FDA. The agency should follow the process defined in Public Law 104-180 and go forward as rapidly as possible with implementing The Action Plan by regulation. Giving the private sector a "free-ride" until 2006 to meet the goals of The Action Plan would be irresponsible.

ENDNOTES

1. Citizens' Petition to Immediately Stop the Distribution of Dangerously Misleading Prescription Drug Information to the Public, June 9, 1998. Accessed July 10, 2002 at www.citizen.org/publications/release.cfm?ID=6639.

2. Svarstad BL, Mount JK. Evaluation of Written Prescription Information Provided in Community Pharmacies, 2001. Final Report to the U.S. Department of Health and Human Services and the Food and Drug Administration, December 21, 2001. Accessed on July 8, 2002 at www.fda.gov/cder/reports/prescriptionInfo/default.htm.

3. Action Plan for the Provision of Useful Prescription Medicine Information presented to the Honorable Donna E. Shalala, Secretary of the Department of Health and Human Services by the Steering Committee for the Collaborative Development of a Long-Range Action Plan for the Provision of Useful Prescription Medicine Information, December 1996.

A Steering Committee, Public Citizen was a member, met seven times between September 18, 1996 and December 4, 1996 in the Washington DC area in a very contentious debate to develop The Action Plan. Consumer groups advocated for the mandatory distribution by pharmacists of FDA regulated drug information similar to regulations first proposed by the agency in 1979. Consumer groups noted that the private sector had pursued a failed paradigm since the inception of the National Council on Patient Information and Education (NCPIE) in 1982 that has not provided useful information to prescription drug consumers. Entities representing the drug industry, pharmacy and medicine, and commercial information vendors pressed for the status quo – voluntary distribution, voluntary quality standards, no oversight, and no FDA involvement.

4. Department of Health and Human Services. Food and Drug Administration. Prescription Drug Product Labeling; Medication Guide Requirements. *Federal Register* Vol. 60, No. 164, Thursday, August 24, 1995.

5. Food and Drug Administration. Prescription Drug Products: Patient Labeling Requirements. *Federal Register* Vol. 44:40016, July 6, 1979.

6. Department of Health and Human Services. Food and Drug Administration. Prescription Drug Product Labeling; Medication Guide Requirements. *Federal Register* Vol. 60, No. 164, Thursday, August 24, 1995, pages 44193 and 44194.

7. Cavuto NJ, Woosley RL, Sale M. Pharmacies and prevention of potentially fatal drug interactions. *Journal of the American Medical Association* 1996;275:1086-7 [letter].

8. Seldane (terfenadine) Professional Product Labeling revised January 1993.

9. Seldane (terfenadine) Professional Product Labeling revised May 1993.

10. Sasich LD, Wolfe SM. Deficiencies in patient information leaflets concerning gastrointestinal complications of nonsteroidal anti-inflammatory drugs. *Journal of General Internal Medicine* 1997;12(suppl):79[abstract].

11. Bradley LR, Sasich LD. The information content of patient medication information leaflets: examination of five fluoroquinolone antibiotics. *Journal of the American Pharmaceutical Association* 1998;38:278-279[abstract].

12. Public Citizen's Comments on the Status of Useful Written Prescription Drug Information for Patients: An 8-State Survey. Accessed on July 10, 2002 at www.citizen.org/publications/release.cfm?ID=6713.

13. Svarstad BL, Bultman DC. Evaluation of Written Prescription Information Provided in Community Pharmacies: An 8-State Study, December 21, 1999. Accessed July 10, 2002 at www.fda.gov/cder/calendar/meeting/rx2000/report1.htm.

14. *Physicians' Desk Reference 54th ed.,* 2000, page 572.

15. *Physicians' Desk Reference 54th ed.,* 2000, page 1368.

16. *Physicians' Desk Reference 54th ed.,* 2000, page 2254.

17. *Physicians' Desk Reference 54th ed.,* 2000, page 2271.

18. Pines WL. A History and Perspective on Direct-to-Consumer Promotion. *Food and Drug Law Journal* 1999;54:489-518.

19. Senator Michael D. Crapo (R-ID) introduced the Pharmacist's Patients Protection Act of 1999 on May 20, 1999. This proposed legislation would have prohibited the FDA from using appropriated funds to implement the 1995 proposed Medication Guide rule, a final 1998 scaled back Medication Guide rule, or any corresponding similar regulation or ruling (including a policy statement or guideline).

In April 1996, then Representative Crapo (R-ID) introduced a bill that would have prohibited the FDA from using appropriated funds to implement the 1995 proposed Medication Guide rule.